

REMARKS/ARGUMENTS

The Office rejected the claims as anticipated in view of a publication to Wang (*J. Chem. Research* (S), 2000, pp. 536-537). It is the Office's opinion that Wang's disclosure of copper catalyzed cross coupling of alkynes under microwave irradiation anticipates the presently claimed process. Applicants traverse the rejection on the grounds that Wang does not disclose or suggest the process of the present claims.

The invention of Claim 1 requires the reaction of an organic halogen compound of formula X-Hal (Ia) with an alkyne of formula $\text{H-C}\equiv\text{C-Y}$ (Ib). The halogen atom of the organic halogen compound is chlorine or bromine. At best, Wang discloses reactions of an organic iodide compound. Wang does not disclose or suggest a reaction whereby chloro- or bromo-organic halogen compounds are reacted with an alkyne.

Wang cannot anticipate the present claims because Wang does not disclose at least one limitation of the presently claimed invention. Applicants thus request withdrawal of the rejection.

Applicants draw the Office's attention to the paragraph bridging pages 1 and 2 of the present specification. The relevant disclosure is reproduced below for convenience.

Investigations of solvent-free reactions of aryl, heteroaryl and vinyl iodides with terminal alkynes in the presence of palladium/copper(I) iodide/triphenylphosphine and potassium fluoride supported on aluminum oxide under the action of microwave radiation have been carried out by G.W. Kabalka et al. (*Tetrahedron Lett*, 41, 2000, p. 5151-5154). The authors mention (p. 5152) that aryl chlorides and bromides did not react and that the starting materials were recovered unchanged.

Applicants submit herewith a copy of the publication by Kabalka. It is readily evident that chlorides and bromides do not react with terminal alkynes in the same way as iodides. In fact, according to the Kabalka publication chloro- and bromo-organics do not react at all with terminal alkynes. On page 1, lines 31-41 of the original specification applicants even pointed out that the disclosure of Wang is different from the presently claimed invention. Applicants

submit that the presently claimed invention is not obvious over the prior art relied on by the Office as evidenced by Kabalka's disclosure that chloro- and bromo-organic radicals do not react with terminal alkynes in the way that iodo-organic radicals do.

The Office further rejected the claims for lack of enablement under 35 U.S.C. § 112, first paragraph. The Office set forth a series of factors for determining whether the enablement requirement is met (see page 3, first full paragraph of the May 4, 2007 Office Action). The Office then went through a *pro forma* exercise to conclude that each of the aforementioned factors was met. Applicants note that the Office did not rely on any objective evidence whatsoever. The Office merely noted each factor and then stated in a conclusory manner that the claimed invention was not enabled.

Applicants submit that the prior art of record provides objective evidence that the originally presented invention is enabled. The publication to Wang discloses that the reaction of an organic halide with a terminal alkyne may take place under various conditions, including various substitutions of the alkyne or halide. In fact, Wang even goes so far to state that the reaction is "a useful tool for preparation of unsymmetrical acetylenes and is now widely used for synthesis of biologically active enyne-compounds" (see the first column, lines 2-3 of Wang). Of course, Wang is disclosing a different type of reaction; namely, one in which microwave irradiation is not used to effect reaction between an organic halide and a terminal alkyne. Nonetheless, Wang makes it clear that aryl halide/terminal alkyne reactions are widely known and used. Further, Wang provides a series of references to support this disclosure. Wang even demonstrates that coupling reactions may be carried out with aryl iodides having organic radicals of very different character, e.g., alkynes, aryl groups, halide-substituted groups, heteroatom-substituted groups, etc. (see Table 1 on page 537 of Wang).

The Office provided absolutely no objective evidence whatsoever that the claimed invention was not enabled. In contrast, applicants have identified and brought to the Office's

attention objective evidence that organic halide/terminal alkyne reactions may be carried out using a broad spectrum of substituted compounds.

Thus, Wang shows that those of skill in the art know that halo exchange reactions may be carried using conventional conditions (e.g., not microwave irradiation) for organic compounds which may be substituted with a variety of hydrocarbon groups. Wang demonstrates that there is a degree of predictability that a coupling reaction may occur even for differently substituted organic halides and/or terminal alkynes. Therefore the scope of enablement provided by the examples of the specification and the disclosure of the original specification should be broadly interpreted (see M.P.E.P. § 2164.03).

It appears that the Office is rejecting the claims for lack of enablement based solely upon the breadth of the claims. Contrary to the Office's unsupported assertion in paragraph no. 6 on page 4 of the May 4 Office Action stating that "there is no valid chemical reasoning for one trained in the art to expect that one can arrive at a compound wherein X and Y any radical with any substituents", Applicants have pointed out that there is in fact valid chemical reason to believe that the claimed subject matter is enabled, e.g., the disclosure of Wang.


For the reasons discussed above, Applicants submit that all now-pending claims are in condition for allowance. Applicants request withdrawal of the rejection and a mailing of a Notice of Allowance acknowledging the patentability of the presently claimed subject matter.

Respectfully submitted,

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LETTERS

Rapid microwave-enhanced, solventless Sonogashira coupling reaction on alumina

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Abstract

A microwave-enhanced, solventless Sonogashira coupling reaction has been developed. Terminal alkynes couple with aryl or alkenyl iodide on palladium-doped alumina in the presence of triphenylphosphine and cuprous iodide to provide high yields of products. © 2000 Published by Elsevier Science Ltd.

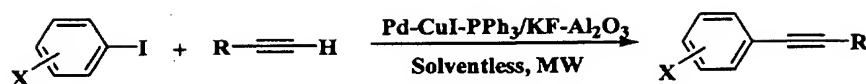
Keywords: coupling reactions; palladium; microwave heating; alkynes.

The Sonogashira coupling reaction of terminal alkynes and aryl or alkenyl halides provides an efficient route to aryl alkynes.¹⁻⁴ Numerous applications to natural product syntheses have been reported, including the construction of complex enediyne antibiotics.⁵⁻⁷ The reaction is generally carried out in organic solvents such as amines, benzene, THF and DMF along with complex palladium catalysts which are soluble in these solvents. These soluble palladium reagents tend to be expensive and sometimes difficult to manipulate and recover. The solvents also pose recyclability (waste handling) problems of their own. In addition, amines such as piperidine, diethylamine and triethylamine are required in most Sonogashira reactions and they add to the environmental burden.

We have found alumina to be a particularly useful reagent in organic synthesis because it can be modified in a variety of ways which enhance its reactivity and it can be utilized to solve some of the environmental problems associated with organic reagents.^{8,9} For example, using a commercially available alumina potassium fluoride mixture, to which we added palladium powder (the least expensive form of palladium available), we were able to carry out Suzuki reactions on a wide variety of aromatic moieties without the use of solvents.⁹

Microwave irradiation of organic reactions has gained in popularity in recent years since it was found to accelerate a wide variety of transformations.^{10,11} We now wish to report a microwave enhanced, energy efficient modification of a solid-state, Sonogashira reaction which enhances the reaction's eco-friendly attributes. The new methodology couples microwave irradiation with a solid-state, solvent free approach and leads to enhanced yields of the desired aryl alkynes.

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The results are summarized in Table 1. The data indicate that, under microwave irradiation in solvent free conditions, coupling readily occurs between a variety of aryl iodides, heteroaromatic iodides and vinyl iodides with terminal alkynes. However, aryl bromides and aryl chlorides do

Table 1
Sonogashira coupling reaction of organic halides with alkynes^a

Entry	RX	RC/CH	Product ^b	Yield(%) ^c
a				94 0 ^d , 0 ^e , 0 ^f 20 ^g
b				84 ^h
c				91
d				97 ^h
e				93 ^h
f				84 ^h
g				96 ^h
h				82
i				67
j				82
k				82
l				84 ^h

^aReaction conditions: aryl or alkenyl iodide (1.00 mmol), alkyne (1.05mmol), Pd powder (40mg), CuI (70 mg), PPh₃ (180mg), KF (40% by weight)/Al₂O₃ (1.0 g). A 1000 watt microwave oven (Sharp Model R-4A38) was used at 100% power for 2.5 minutes. ^bAll reaction products exhibited physical and spectral characteristics in accord with literature values. ^cIsolated yields. ^dNo palladium was added. ^eNo triphenylphosphine was added. ^fNo CuI was added. ^gNo alumina was added and the 1000 watt microwave oven was used at 30% power for 3 minutes. ^hSatisfactory elemental analysis was obtained.

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not react and the starting materials are recovered unchanged. Substituent effects were also examined. The results indicate that an electron-donating group on the aromatic ring enhances the reaction and leads to the desired product in excellent yields (97 and 93%, respectively, entries d and e). Strong electron-withdrawing groups, lead to more moderate yields (82 and 67%, respectively, entries h and i). It is interesting to note that a bulky group on the *ortho*-position of the benzene ring did not inhibit the reaction (82%, entry k).

During the investigation, we found that the reaction did not occur in the absence of palladium, cuprous iodide, or triphenylphosphine (entry a). CAUTION, the microwave reaction should not be attempted in the absence of alumina which apparently acts as a temperature moderator.¹² Without alumina, the liquid reactants can react uncontrollably in the presence of metallic palladium (DANGER).

Larock and his co-worker have reported that indoles and benzofurans can be prepared by the coupling terminal alkynes with *o*-iodoaniline and *o*-iodophenol, respectively, using palladium and copper reagents.^{13,14} We found that coupling *o*-iodophenol with terminal alkyne produced the cyclized product, benzofuran, in moderate yield. The coupling reaction of *o*-iodoaniline with terminal alkynes is dependent on the reaction conditions. If a 1:1 ratio of *o*-iodoaniline to alkyne is used, only the coupling product is obtained, and no cyclization product forms. This differs from previously reported results.¹⁴ When the ratio of *o*-iodoaniline to alkyne is 2:1, a mixture of cyclization and coupling products is formed (Fig. 1).

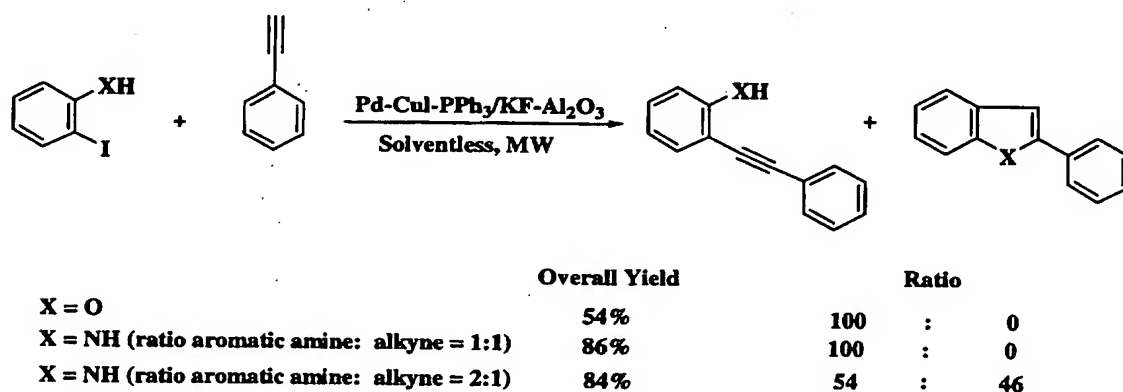


Figure 1.

The synthesis of 1-phenyl-1-decyne is representative. Iodobenzene (0.204 g, 1.000 mmol) and 1-decyne (0.145 g, 1.050 mmol) were added to a mixture of KF/Al₂O₃ (1.000 g, 40% by weight), palladium powder (0.040 g, 0.376 mmol, 99.9+% as a submicron powder), cuprous iodide (0.070 g, 0.368 mmol) and triphenylphosphine (0.180 g, 0.686 mmol) contained in a clean, dry, 25 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum (punctured by an 18 gauge needle), placed in the microwave and irradiated at 100% power for 2.5 min. After cooling, hexane (5 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The mixture was vacuum filtered using a sintered glass funnel and the product was purified by flash chromatography to yield 0.201 g of 1-phenyl-1-decyne (94%). The same reaction was carried out on a 10 mmol scale and resulted in slightly higher yields.

In summary, a reliable, rapid and practical procedure for the synthesis of arylacetylenes via a Sonogashira coupling reaction was developed which involves the use of a solvent-free mixture of potassium fluoride on alumina under microwave irradiation conditions. The reaction is environmentally friendly, and results in high yields of the desired product.

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Abstract

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